

## TRANSMITTAL LETTER TO THE UNITED STATES

BFE-5407 US

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

09/890419

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/EP00/00130

7 January 2000

29 January 1999

TITLE OF INVENTION

CARTRIDGE FOR DIALYSIS CONTAINING SODIUM BICARBONATE

APPLICANT(S) FOR DO/EO/US

Mario MAZZA and Giampiero PESCI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

## Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☒ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Copy of Written Opinion;

Copy of Response to Written Opinion; and

Return Receipt Postcard.

U.S. APPLICATION NO. (IF KNOWN) SEE 37 CFR <b>097/890419</b>	INTERNATIONAL APPLICATION NO. <b>PCT/EP00/00130</b>	ATTORNEY'S DOCKET NUMBER <b>BFE-5407 US</b>
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21. The following fees are submitted:				<b>CALCULATIONS PTO USE ONLY</b>	
<b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :</b>					
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO .....				\$1,000.00	
<input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO .....				\$860.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....				\$710.00	
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) .....				\$690.00	
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) .....				\$100.00	
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>\$860.00</b>	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30				<b>\$0.00</b>	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	25 - 20 =	5	x \$18.00	<b>\$90.00</b>	
Independent claims	4 - 3 =	1	x \$80.00	<b>\$80.00</b>	
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$1,030.00</b>	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). <input type="checkbox"/>				<b>\$0.00</b>	
<b>SUBTOTAL =</b>				<b>\$1,030.00</b>	
Processing fee of <b>\$130.00</b> for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30 +				<b>\$0.00</b>	
<b>TOTAL NATIONAL FEE =</b>				<b>\$1,030.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input checked="" type="checkbox"/>				<b>\$40.00</b>	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$1,070.00</b>	
				<b>Amount to be refunded</b>	\$
				<b>charged</b>	\$

- ☒ A check in the amount of **\$1,070.00** to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \_\_\_\_\_ to cover the above fees.  
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **02-1818** A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

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REGISTRATION NUMBER

July 27, 2001

DATE

CARTRIDGE FOR DIALYSIS CONTAINING SODIUM  
BICARBONATE

5 This invention relates to dialysis cartridges containing solid sodium bicarbonate.

**BACKGROUND**

It has long been known to use cartridges containing drugs, or other  
10 substances, in solid form and to pass water or a solution through the cartridge to dissolve the solid substance continuously, e.g. for continuous administration to a patient.

Examples are WO-A-86/03417 and US-A-4432756.

It is also known, as disclosed in EP-A-0278100 to provide sodium  
15 bicarbonate in solid form for use as a buffer in haemodialysis. Sodium bicarbonate is stored separately from the rest of a dialysis solution, which contains calcium and magnesium ions, to prevent calcium and magnesium carbonate precipitation. A cartridge of sodium bicarbonate powder is inserted in a haemodialysis machine and water is passed through the  
20 cartridge. The powder is gradually dissolved, so that a solution of sodium bicarbonate is continuously produced. The solution is continuously flowed through the machine, mixing with the rest of the dialysis solution in-line upstream of the dialyzer. There is, therefore, only a short dwell time in the machine after mixing, so that the problem of calcium and  
25 magnesium carbonates being precipitated is avoided.

A problem does, however, arise with such cartridges. The pH of the mixed dialysis solution is monitored upstream of the dialyzer. If the pH falls outside a given range, then an alarm is triggered. It has been found that this often happens during the first twenty minutes of flow,  
30 when the machine is being set up for operation. After this period, no

problems are encountered. This causes substantial inconvenience to personnel operating haemodialysis machines, since the problem has to be investigated and the machine reset, each time the alarm is triggered.

5       The inventors have discovered that the problem is probably caused by contamination of the sodium bicarbonate powder with a small amount of sodium carbonate. The bicarbonate is less soluble than the carbonate, so that a high pH is caused by the dissolution of the carbonate in the early stages. Once the carbonate has dissolved, the problem disappears. It is,  
10       however, difficult and expensive to produce a sodium bicarbonate powder, which is not contaminated with sodium carbonate.

          A possible solution to the problem once it was realised that sodium carbonate precipitation was the cause, would be to introduce a further line  
15       upstream of the pH monitoring device to add dilute acid solution to the dialysis solution during the first twenty minutes of use of the cartridge. This could be done upstream or downstream of the cartridge. This involves, however, modification of the dialysis solution, use of an additional solution and additional operational control.

20

          The inventors have found that the problem can be relatively simply solved by modifying the contents of the cartridge.

### SUMMARY OF THE INVENTION

25       The present invention relates to a cartridge having an openable sealed inlet and an openable sealed outlet, for connection in-line in a haemodialysis machine for passage of water, or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form.

In accordance with the invention, the cartridge additionally contains an acid, or acid anhydride in solid form, or carbon dioxide gas.

When the cartridge is mounted in a haemodialysis machine and  
5 water is passed through the cartridge, the acid or acid anhydride (including carbon dioxide) is gradually dissolved, decreasing the pH of the resulting solution to counteract any temporary increase in pH caused by sodium carbonate contamination.

10 The amount of acid or acid anhydride provided is preferably predetermined, so that it is leached from the cartridge during the initial 10 to 30 minutes, i.e. during the period that sodium carbonate is also likely to be leached from the cartridge.

15 Carbon dioxide may be added to the cartridge, during manufacture, in solid form, i.e. as dry ice, prior to sealing the cartridge.

Acids which may be used in solid form may be organic acids, e.g. citric acid, or tartaric acid, citric acid being preferred for clinical  
20 acceptability.

The cartridge may contain at least 0.2g of acid, or acid anhydride per 1000g of sodium bicarbonate; preferably at least 0.5g per 1000g and most preferably at least 1g per 1000g. The preferred embodiment  
25 contains 2.7g per 1000g.

### DRAWINGS

The invention is described with reference to the accompanying drawings, wherein:-

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Fig 1. is a side elevation of a cartridge according to the invention, shown partly in cross-section; and

Fig 2. is a diagrammatic illustration of the cartridge of fig 1 connected in a haemodialysis machine.

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### PREFERRED EMBODIMENTS

The currently preferred embodiments of the invention are now described. The construction of haemodialysis machines is well known, as is the construction of a sodium bicarbonate cartridge for use in a haemodialysis machine. The machine and the cartridge are not, therefore, described in detail. The cartridge may be of the type sold under the trademark EASYCART by Bieffe Medital S.p.A. of Italy.

The cartridge 10 comprises a body 14, closed by a lid 15 and defining a chamber 11. The body and lid are injection moulded in polypropylene. The chamber 11 contains sodium bicarbonate in granular, crystalline form, although other solid forms are possible. The lid 15 is sealed to the body 14 by ultrasonic welding. The lid 15 has an inlet 12 and the body had an outlet 13, both sealed closed in the as-moulded state, by integral membranes 17, 18 respectively.

The cartridge 10 is connected in-line in a first line 20 for receiving deionised water at 21 and supplying sodium bicarbonate solution to a main line 22, at 23. The membranes 17, 18 are perforated during clamping of the cartridge into the machine, by piercing means provided on the machine. The main line 22 also receives deionised water at 24. A container 30, containing a solution of the other ingredients of a dialysis solution, is connected to the main line 22 by a second line 25 at 26. A final dialysis solution is formed at point 26 and the main line 22 feeds this

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to a dialyzer 40. A pH detector 50 is connected to the main line 22 downstream of point 26 and upstream of the dialyzer. The detector is connected with a control system (not shown), which produces an alarm, if a pH outside a predetermined range is exceeded. This range is usually 6.8  
5 to 7.9 pH may be monitored by other means, such as by conductivity measurement.

The solution in the container 30 may contain any of the components usually provided in a dialysis solution, such as calcium and magnesium  
10 chloride, sodium chloride and an osmotic agent, such as dextrose.

In accordance with the present invention, the cartridge contains, in addition to the sodium bicarbonate, an acid or acid anhydride in solid form, or carbon dioxide gas, so as to avoid any sodium carbonate  
15 contamination causing a temporary increase in the pH of the dialysis solution to a degree sufficient to exceed the predetermined threshold and trigger an alarm.

The preferred embodiment of a cartridge contains 750g sodium  
20 bicarbonate and 2g citric acid, both in granular, crystalline form. A similar weight ratio could be used with different amounts of sodium bicarbonate.

Alternatives to citric acid are preferably provided in the same  
25 weight ratio.

Tests were carried out using cartridges containing 750g sodium bicarbonate and citric acid, tartaric acid, or carbon dioxide (added as dry

6

ice) respectively. These were compared with similar cartridges, to which no acid or carbon dioxide had been added.

The tests were carried out by running an Integra (trademark) haemodialysis machine, using the various cartridges. Notes were made of which cartridges produced an alarm signal, due to the pH of the mixed dialysis solution falling outside the predetermined range. The actual maximum pH of each solution was also recorded. "Acid" solutions, ie the solutions carrying the other components of the dialysis solution, were standard solutions produced by Gambro. In each case, the pH of the water supplied was 6.1. The results are shown in the tables below. There were numerous false alarms with the reference cartridges, but no false alarms with the cartridges according to the invention.

15 Table 1

This shows the results using the reference cartridges, containing 750g sodium bicarbonate and no added acid or carbon dioxide.

Sample No.	Maximum pH of dialysis solution	Alarm Yes/No
1	7.9	No
2	7.8	No
3	8	Yes
4	8.1	Yes
5	7.9	No
6	8	Yes
7	8.2	Yes
8	8	Yes
9	7.4	No
10	7.4	No



Table 2

This shows the results using cartridges according to the invention, containing 2g citric acid and 750g sodium bicarbonate.

5

Sample No.	Maximum pH of dialysis solution	Alarm Yes/No
11	7.5	No
12	7.5	No
13	7.5	No
14	7.5	No
15	7.4	No
16	7.4	No
17	7.4	No
18	7.4	No
19	7.4	No
20	7.4	No
21	7.4	No

Table 3

This shows the results using cartridges according to the invention, containing 0.5g or 1g of carbon dioxide (dry ice) and 750g sodium bicarbonate.

10

Sample No.	Amount of CO <sub>2</sub> (g)	Maximum pH of dialysis solution	Alarm Yes/No
22	0.5	7.5	No
23	1.0	7.3	No
24	0.5	7.5	No
25	1.0	7.3	No
26	1.0	7.3	No

Table 4

This shows the results using cartridges according to the invention, containing 1g tartaric acid and 750g sodium bicarbonate.

5

Sample No.	Maximum pH of dialysis solution	Alarm Yes/No
27	7.5	No
28	7.5	No

Other tests were carried out using different "acid" solutions, and water of different pH. In each case, a cartridge according to the invention did not cause any alarm due to either high or low pH.

10

### Claims:

1. A cartridge having an openable, sealed inlet and an openable, sealed outlet for connection in-line in a haemodialysis machine for passage of water or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form,

characterised in that the cartridge additionally contains an acid or acid anhydride in solid form or carbon dioxide gas in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge.

2. A cartridge according to Claim 1, wherein the acid is in powder form.

3. A cartridge according to Claim 1 or Claim 2, wherein the acid is citric acid.

4. A cartridge according to Claim 1 or Claim 2, wherein the acid is tartaric acid, or another organic acid.

5. A cartridge according to any one of the preceding claims containing at least 0.2g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

6. A cartridge according to Claim 5, wherein the cartridge contains at least 0.5g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

7. A method of preventing a temporary increase of pH in a dialysis solution being continuously produced in a haemodialysis machine from different component sources including a cartridge containing solid sodium

AMENDED SHEET

bicarbonate, the method comprising including in the cartridge an acid or acid anhydride in solid form, or carbon dioxide gas.

8. A method according to Claim 7, wherein the cartridge and its contents are in accordance with any one of Claims 1 to 6.

9. A method of introducing carbon dioxide gas to a cartridge according to Claim 1, wherein the carbon dioxide is introduced as dry ice.

10. A haemodialysis machine comprising a cartridge as claimed in any one of Claims 1 to 6 which is connected in-line.

1/2

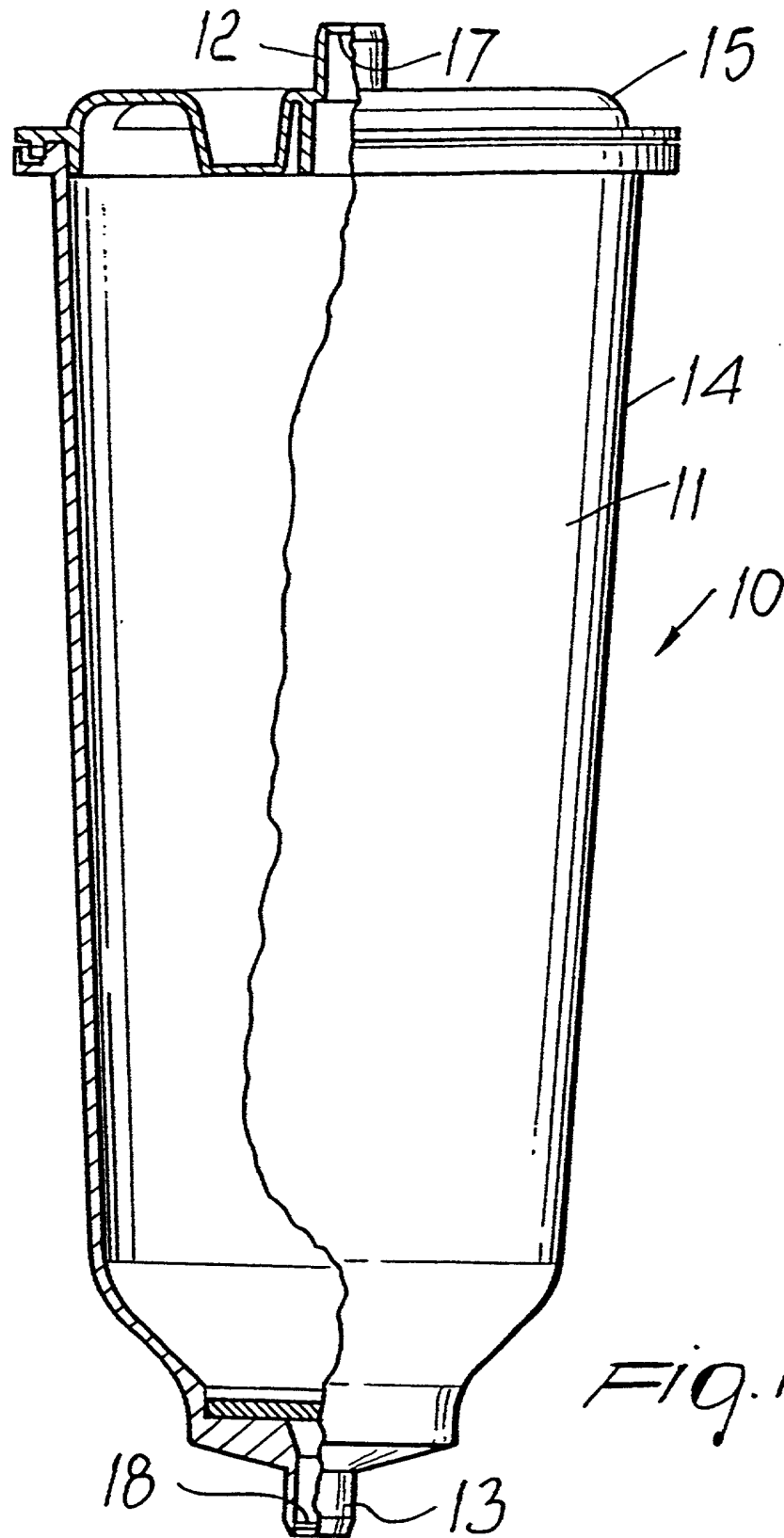


Fig. 1

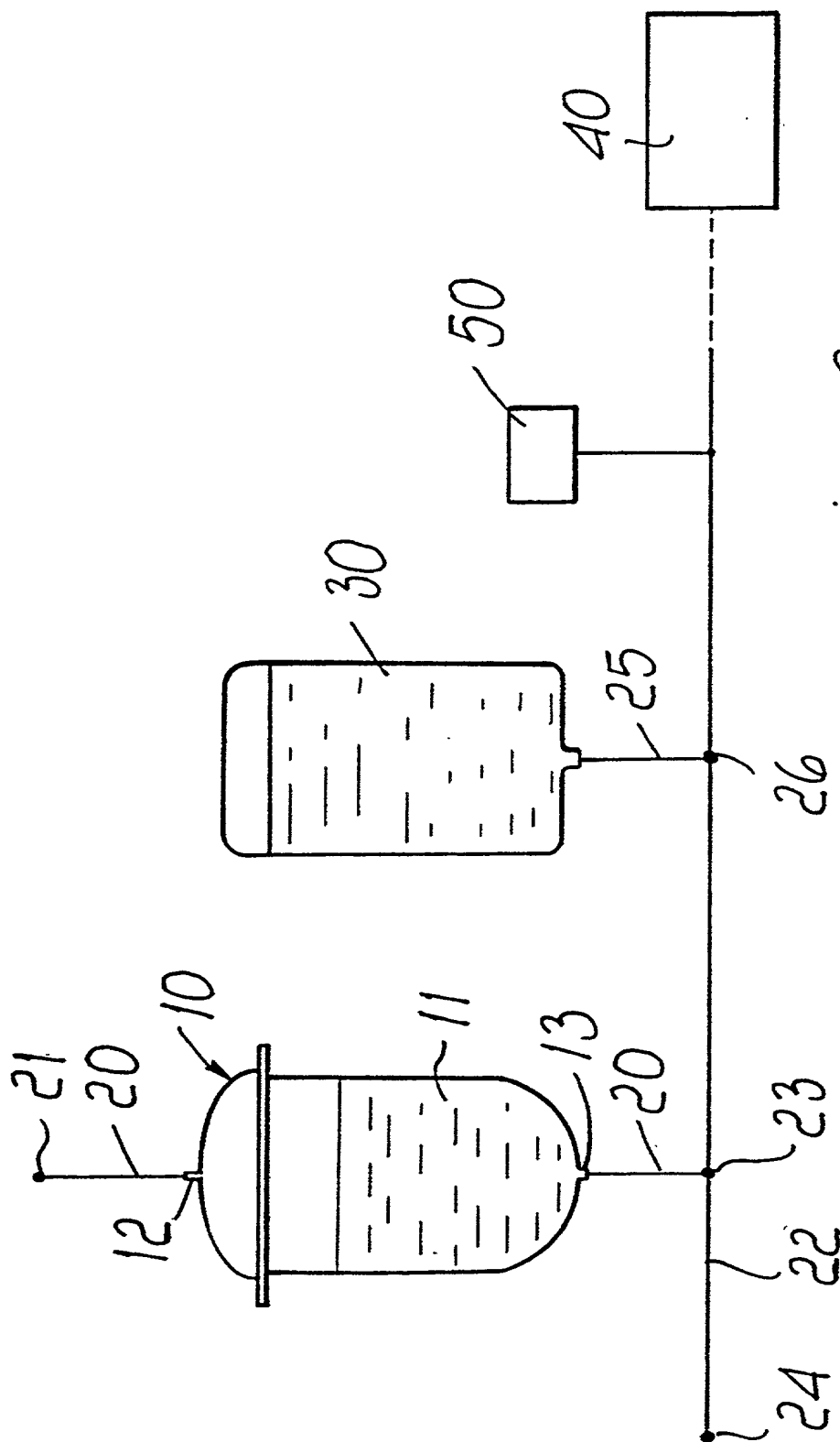


Fig. 2

Docket No.  
BFE-5407 US

## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled  
**CARTRIDGE FOR DIALYSIS CONTAINING SODIUM BICARBONATE**

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 7 January 2000 as United States Application No. or PCT International Application Number PCT/EP00/00130 and was amended on \_\_\_\_\_

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

<u>PCT/EP00/00130</u>	<u>WIPO</u>	<u>7 January 2000</u>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	
<u>MI99A00176</u>	<u>Italy</u>	<u>29 January 1999</u>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	
_____	_____	_____	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

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